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Sleep benefit in Parkinson's disease is associated with short sleep times

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Abstract

Sleep benefit in Parkinson's disease is characterized by restoration of mobility upon awakening from sleep and prior to drug intake. With this study, we aimed at assessing clinical and nocturnal sleep correlates of this phenomenon. We recorded motor and non-motor symptoms in 131 Parkinson patients with and without sleep benefit, as assessed by questionnaires. Polysomnography recordings were performed in 60 of these patients. Thirty-nine Parkinson patients (30%) reported sleep benefit. Motor symptoms, measures of sleepiness, fatigue, depression, anxiety, sleep-wake disorders, and dopaminergic treatment were not associated with sleep benefit, and most polysomnography measures were similar between both groups. However, Parkinson patients with sleep benefit had shorter total sleep times and longer sleep latencies at nocturnal polysomnography. The link between the occurrence of sleep benefit and shorter nocturnal sleep in Parkinson's disease remains unclear.

Introduction

After nocturnal sleep, many patients with Parkinson's disease (PD) suffer from marked hypokinesia which can only be relieved by intake of dopaminergic drugs. In contrast, other PD patients report sleep benefit which has been defined as "restoration of mobility on awakening from sleep prior to drug intake" [1]. Sleep is believed to improve extrapyramidal motor functions of these patients. In a consecutive series of 312 PD patients who were examined by means of a structured questionnaire, Merello and colleagues found sleep benefit after nocturnal sleep in 55% of these patients, particularly in those with long disease duration, and 21% were able to reduce medication because of this phenomenon [2]. After daytime naps, 25-34% of PD patients reported sleep benefit [2,3]. The mean duration of sleep benefit after nocturnal sleep was 85 minutes, but there were large individual differences (range 3-300 minutes). Another study found a similar mean duration of sleep benefit [4]. Other studies found sleep benefit in 33-42% of PD patients [5,6].

Although there appears to be a striking dichotomy of PD patients with and without sleep benefit, not much is known of the motor, non-motor and sleep associates of sleep benefit in PD. In particular, there are only few data on polysomnographic measures of sleep benefit [7]. Thus, with the present study we aimed at comparing PD patients with and without sleep benefit in relation to characteristics of PD and to actigraphy and polysomnographic sleep measures.

Methods

This study consisted of prospective assessment of data on sleep benefit, and correlation with PD characteristics and video-polysomnography and actigraphy measures. The latter were analyzed retrospectively, if available. Polysomnography recordings in PD patients were primarily done when REM sleep behavior disorder or sleep apnea were suspected, or in the

presence of excessive daytime sleepiness. Actigraphy recordings were performed upon availability of actimeters. The study was approved by the local ethical committee, and all patients consented in participating.

We contacted 185 patients who were examined in our outpatient clinic during the last 6 months and asked the following question: "In the morning after awakening and before intake of your first Parkinson pill, do you usually remark clear improvement of your motor symptoms, e.g. of the slowness, the shaking or the muscle stiffness, as compared to other times during the day when the medication fades off?". Finally, 173 patients consented in participating in the study and were classified as patients with or without sleep benefit.

Thereafter, they received an extensive questionnaire which included validated scales such as the Epworth sleepiness scale (ESS), the fatigue severity scale and the Hospital Anxiety and Depression Scale (HADS). Questionnaires were completely filled in and returned by 131 patients (71% of the contacted population). In these patients, we assessed demographic data, type of PD (akinetic-rigid versus tremor-dominant PD), predominant side of symptoms (right versus left), PD duration, presence of motor fluctuations, and medication including dopaminergic drugs, neuroleptics, and antidepressants.

Polysomnography recordings were available in 60 of 131 patients (46%) and performed as described before [8]. Briefly, conventional overnight polysomnography (using a 16-channel recording system: Embla A10) was performed from 11 p.m. to 7 a.m. We scored sleep stages according to standard criteria [9]. Sleep variables included sleep onset latency, defined as the time from lights off to the first epoch of stage 2 sleep; REM latency, i.e. the time from sleep onset and the occurrence of the first REM sleep epoch; total sleep time; sleep efficiency, i.e. time asleep as a percentage of time from sleep onset until lights on; percentage of TST spend in different sleep stages. Furthermore, we assessed the apnea-hypopnea index and periodic limb movements during sleep. Last not least, REM sleep behavior disorder and REM sleep without atonia were diagnosed according to previous recommendations [10,11].

Of patients submitted to polysomnography, 38 were also examined with actigraphy recordings and sleep logs. Actigraphy was performed as described before, with patients wearing the actiwatch on their non-dominant wrist for 2 weeks [8]. In patients with unilateral tremor, the device was worn on the contralateral wrist.

Differences between groups were computed with non-parametric tests when appropriate, including the Mann-Whitney test. Otherwise, Student's t-test was used for comparisons of means. To control for the influence of covariates, we performed a multiple regression analysis with the dependent variable sleep benefit versus the independent variables age, sex, periodic limb movement index, apnea-hypopnea index, presence of REM sleep behavior disorder, sleep latency, and total sleep time. All statistical analyses were made with SPSS version 19.

Results

Thirty-nine patients (30%) reported sleep benefit (Table 1). In these patients, the interval between awakening in the morning and first dopaminergic drug intake was much longer than in those without sleep benefit. Demographic data and characteristics of PD did not differ between patients with and without sleep benefit. Duration of the nocturnal sleep episode on actigraphy was shorter in PD patients with sleep benefit (6.6 ± 0.9 versus 7.1 ± 0.8 hours), but this result failed to be significant ($p=0.07$). Furthermore, patients with recorded daytime naps were present in both groups ($p=0.4$). Although all patients were given the same time interval to sleep during polysomnography, our recordings revealed shorter total sleep times (272 ± 116 versus 346 ± 74 minutes, $p=0.03$) and longer sleep latencies (81 ± 87 versus 26 ± 20 , $p=0.02$) in patients with sleep benefit. The finding of shorter total sleep times remained significant in a multiple regression analysis. All other parameters including percentages of slow wave and REM sleep, measures of breathing disorders and periodic leg movements during sleep, and the frequencies of REM sleep behavior disorder and of REM sleep

without atonia were similar in both groups. We found no association between polysomnographic findings related to REM sleep behavior disorder and sleep benefit.

Discussion

We found that PD patients with sleep benefit had shorter total sleep times and longer sleep latencies than those without. To date, there exists only one polysomnography study in 20 PD patients, which found similar results, but these did not reach significance, probably because strength was not high enough [7]. The authors found tendencies towards shorter sleep times, lower sleep efficiencies, more awakenings per hour and higher sleep latencies in PD patients with sleep benefit. Therefore, this previous study supports our surprising finding of an inverse association of sleep duration and sleep benefit. This observation is further supported by actigraphy measures in 38 patients of our study which revealed a tendency towards shorter nocturnal sleep times in PD patients with sleep benefit. These patients, however, did not more often perform daytime naps than those without sleep benefit.

In addition, our study in 131 PD patients showed that neither sleep-wake disturbances such as periodic limb movements during sleep, sleep apnea, and REM sleep behavior disorder nor other non-motor symptoms such as excessive daytime sleepiness, fatigue, depression and anxiety are associated with the presence of sleep benefit. Previous studies focused on motor symptoms and found an association of sleep benefit with longer disease duration, more severe motor symptoms, increased expression of dyskinesia and higher doses of levodopa [4-6]. In our study, we found only a tendency towards more severe motor symptoms in PD patients with sleep benefit, but our cohort was smaller than in some of the previous questionnaire studies. Furthermore, some authors found that younger age at disease onset was linked to an increased expression of sleep benefit [6]. This was not found in the present cohort.

The unknown underlying mechanism of sleep benefit in PD was discussed before [5, 7].

Sleep might have an effect on the dopaminergic system, e.g. on accumulation or storage of dopamine, or on remodeling of dopamine receptors [7]. On the other hand, it is possible that sleep modulates signaling within the basal ganglia, e.g. the beta oscillations in the human motor system which are associated with normal movement suppression and motor impairment in PD [12]. The seemingly paradoxical association of shorter sleep duration and the presence of sleep benefit, however, is not easily explained by these theories.

Thus, our finding may raise some doubts about a direct causal link between morning motor improvement and preceding sleep and about the adequacy of the term 'sleep benefit'. Why would less sleep be more beneficial with regard to morning motor symptoms? Similarly counterintuitive is the finding that objectively measured daytime sleepiness is associated with higher sleep efficiency and shorter sleep onset latency at night [13-14]. In other words, PD patients with particularly good nighttime sleep are sleepier at daytime. Altogether, one might conclude that too much sleep may not necessarily be beneficial for PD patients, neither for motor symptoms nor for vigilance.

Last not least, the inverse conclusion that the effect of morning improvement is instead explained by carry-over benefit from previous night's dopaminergic medication cannot be ruled out. Still, it remains unclear whether the difference of one hour sleep may account for the assumed carry-over effect.

Certainly, this study has limitations. Above all, there is no objective measure for sleep benefit. Furthermore, we addressed sleepiness, fatigue, depression and anxiety only by questionnaires. The fact that only PD patients with suspected sleep-wake disorders were examined with polysomnography constitutes a potential inclusion bias.

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